

What is claimed is:

- 1    1. A method for identifying an OP-1 receptor-binding analog, said  
2         analog being characterized as having substantially the same  
3         binding affinity for a cell surface receptor as OP-1, the method  
4         comprising the steps of:
  - 5             (a) providing a sample containing a protein selected from the group  
6                 consisting of:
    - 7                     (i) a polypeptide chain comprising an amino acid sequence  
8                         defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
9                         OP1-binding analog thereof;
    - 10                    (ii) a polypeptide chain comprising an amino acid sequence  
11                         defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
12                         OP1-binding analog thereof;
    - 13                    (iii) a polypeptide chain comprising an amino acid sequence  
14                         defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
15                         OP1 binding analog thereof;
    - 16                    (iv) a polypeptide chain having binding affinity for OP-1 and  
17                         sharing at least 40% amino acid identity with residues 23-  
18                         122 of Seq. ID No. 7 (ALK-6),;
    - 19                    (v) a polypeptide chain having binding affinity for OP-1 and  
20                         encoded by a nucleic acid obtainable by amplification with  
21                         one or more primer sequences defined by Seq. ID Nos. 12-15;  
22                         or
    - 23                    (vi) a polypeptide chain having binding affinity for OP-1 and  
24                         encoded by a nucleic acid that hybridizes under stringent  
25                         conditions with a nucleic acid comprising the sequence  
26                         defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
  - 27             (b) contacting said sample with a candidate OP1 receptor- binding  
28                 analog; and
  - 29             (c) detecting specific binding between said candidate OP1 receptor-  
30                 binding analog and said protein.
- 1    2. A method for identifying an OP-1 receptor-binding analog, said  
2         analog being characterized as having substantially the same  
3         binding affinity for a cell surface receptor as OP1, the method  
4         comprising the steps of:

5                 (a) providing a cell that expresses a surface receptor protein having  
6                 binding specificity for OP-1 selected from the group consisting  
7                 of:  
8                 (i) a polypeptide chain comprising an amino acid sequence  
9                 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
10                OP1-binding analog thereof;  
11                (ii) a polypeptide chain comprising an amino acid sequence  
12                defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
13                OP1-binding analog thereof;  
14                (iii) a polypeptide chain comprising an amino acid sequence  
15                defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
16                OP1 binding analog thereof;  
17                (iv) a polypeptide chain having binding affinity for OP-1 and  
18                sharing at least 40% amino acid identity with residues 23-  
19                122 of Seq. ID No. 7 (ALK-6),;  
20                (v) a polypeptide chain having binding affinity for OP-1 and  
21                encoded by a nucleic acid obtainable by amplification with  
22                one or more primer sequences defined by Seq. ID Nos. 12-15;  
23                or  
24                (vi) a polypeptide chain having binding affinity for OP-1 and  
25                encoded by a nucleic acid that hybridizes under stringent  
26                conditions with a nucleic acid comprising the sequence  
27                defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;  
28                (b) contacting said cell with a candidate OP1 receptor-binding  
29                analog; and  
30                (c) detecting induction of an OP-1-mediated cellular response.  
1                3. The method of claim 2 wherein said OP-1 mediated cellular response  
2                detected in step (c) is induction of a kinase activity, inhibition of  
3                epithelial cell growth, or induction of a cell differentiation  
4                marker.  
1                4. The method of claim 2 or 3 wherein said cell comprises a transfected  
2                nucleic acid comprising a reporter gene in operative association with a  
3                control element derived from an OP-1 inducible protein.  
1                5. The method of any of claims 1-4 wherein said sample further comprises  
2                part or all of a Type II serine/threonine kinase receptor protein  
3                having binding affinity for OP-1, activin or BMP-4.

1       6. A method for producing an OP-1 receptor binding analog, the method  
2 comprising the steps of:

3                   (a) obtaining, by the method of any of claims 1-5, a candidate OP-1  
4                   binding analog, and

5 (b) producing either said candidate analog or a second OP-1 binding  
6 analog derived from said candidate and having substantially the  
7 same OP-1 receptor-binding domain as said candidate.

1    7. The method of producing an OP-1 receptor-binding analog of claim 6  
2        wherein said analog produced in step (b) is by recombinant DNA  
3        techniques, or by nonbiological peptide synthesis.

1       8. A kit for identifying OP-1 or a candidate OP-1 receptor binding analog  
2           in a sample, the kit comprising:

(a) a receptacle adapted to receive a sample and containing a protein selected from the group consisting of:

5 (i) a polypeptide chain comprising an amino acid sequence  
6 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
7 OP1-binding analog thereof;

8                   (ii) a polypeptide chain comprising an amino acid sequence  
9                   defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
0                   OP1-binding analog thereof;

4 (iv) a polypeptide chain having binding affinity for OP-1 and  
5 sharing at least 40% amino acid identity with residues 23-  
6 122 of Seq. ID No. 7 (ALK-6);

7 (v) a polypeptide chain having binding affinity for OP-1 and  
8 encoded by a nucleic acid obtainable by amplification with  
9 one or more primer sequences defined by Seq. ID Nos. 12-15;  
0 or

1 (vi) a polypeptide chain having binding affinity for OP-1 and  
2 encoded by a nucleic acid that hybridizes under stringent  
3 conditions with a nucleic acid comprising the sequence  
4 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6);  
5 and

(b) means for detecting interaction of OP-1 or a candidate OP-1 receptor-binding analog with said protein of part (a), said OP-1

28                   or candidate analog comprising part of said sample provided to  
29                   said receptacle.

1     9.   The kit of claim 8 wherein said means in part (b) comprises either  
2                   (i)   means for detecting specific binding interaction of OP-1  
3                   or said candidate analog with said protein; or  
4                   (ii)   means for detecting induction of an OP-1 mediated cellular  
5                   response.

1     10.   The kit of claim 8 or 9 further comprising a serine/threonine Type II  
2                   receptor having binding specificity for OP-1, activin or BMP-4.

1     11.   An OP-1 receptor-binding analog produced by the method of any of claims  
2                   1-7 or use of the kit of claims 8-10.

1     12.   The analog produced by the method of any of claims 1-8, said analog  
2                   (i)comprising an amino acid sequence sharing greater than 60%  
3                   identity with the C-terminal 96 amino acids of the sequence  
4                   represented by Seq. ID No. 9 (OP-1, residues 335-431), and  
5                   (ii) being substantially incapable of inducing an OP-1 mediated  
6                   cellular response.

1     13.   The analog of claim 11 or 12 further having binding affinity for a  
2                   Type II serine/threonine kinase cell surface receptor.

1     14.   The analog of claim 13 wherein said Type II receptor also has binding  
2                   affinity for activin or BMP-4.

1     15.   An isolated ligand-receptor complex comprising two molecules  
2                   interacting as specific binding partners, the first said molecule  
3                   defining said ligand and comprising at least the C-terminal 96 amino  
4                   acids of OP1 (residues 335-431 of Seq ID No. 9)or a receptor-binding  
5                   analog thereof, and the second said molecule defining said receptor and  
6                   being selected from the group consisting of:  
7                   (i) a polypeptide chain comprising an amino acid sequence  
8                   defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
9                   OP1-binding analog thereof;  
10                  (ii) a polypeptide chain comprising an amino acid sequence  
11                  defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
12                  OP1-binding analog thereof;  
13                  (iii) a polypeptide chain comprising an amino acid sequence  
14                  defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
15                  OP1 binding analog thereof;



1    23.    The use according to claim 22 wherein said OP-1 receptor-binding analog  
2           comprises an antibody having binding specificity for

3                 (i) the ligand binding domain of a cell surface receptor defined  
4                   by Seq. ID Nos. 3, 5, or 7 or an OP-1 binding analog  
5                   thereof; or  
6                 (ii) the receptor binding domain of OP-1, represented by Seq. ID  
7                   No. 9, or a receptor-binding analog thereof.

1    24.    Use of a protein selected from the group consisting of:

2                 (i) a polypeptide chain comprising an amino acid sequence  
3                   defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
4                   OP1-binding analog thereof;  
5                 (ii) a polypeptide chain comprising an amino acid sequence  
6                   defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
7                   OP1-binding analog thereof;  
8                 (iii) a polypeptide chain comprising an amino acid sequence  
9                   defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
10                  OP1 binding analog thereof;  
11                (iv) a polypeptide chain having binding affinity for OP-1 and  
12                   sharing at least 40% amino acid identity with residues 23-  
13                   122 of Seq. ID No. 7 (ALK-6),;  
14                (v) a polypeptide chain having binding affinity for OP-1 and  
15                   encoded by a nucleic acid obtainable by amplification with  
16                   one or more primer sequences defined by Seq. ID Nos. 12-15,  
17                   or  
18                (vi) a polypeptide chain having binding affinity for OP-1 and  
19                   encoded by a nucleic acid that hybridizes under stringent  
20                   conditions with a nucleic acid comprising the sequence  
21                   defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;

22                  in a method for antagonizing

23                 (i) OP-1 binding to a cell surface receptor; or  
24                 (ii) induction of an OP-1 mediated cellular response.

1    25.    A method for antagonizing activin binding to a cell surface receptor,  
2                   the method comprising the step of:

3                   providing a cell expressing a said receptor with a protein having  
4                   binding specificity for the amino acid sequence defined by  
5                   residues 16-123 of Seq ID No. 3 or an OP-1 binding sequence  
6                   variant thereof, said protein sharing at least ,60% amino acid

7 sequence identity with residue 335-431 of the sequence defined by  
8 Seq ID No. 9,

9 such that said protein, when provided to said cell, is competent  
10 to interact specifically with said receptor, thereby  
11 substantially inhibiting activin binding to said receptor.

1 26. A method for antagonizing BMP-4 binding to a cell surface receptor, the  
2 method comprising the step of:

3 providing a cell expressing a said receptor with a protein having  
4 binding specificity for the ligand binding domain defined by  
5 residues 24-152 of Seq ID No. 5 (ALK-3), or residues 23-122 of  
6 Seq ID No. 7 (ALK-6), or an OP-1 binding sequence variant  
7 thereof, said protein sharing at least 60% amino acid sequence  
8 identity with residues 335-431 of the sequence defined by Seq ID  
9 No. 9,

10 such that said protein, when provided to said cell, is competent  
11 to interact specifically with said receptor, thereby  
12 substantially inhibiting BMP-4 binding to said receptor.

1 27. Use of the OP-1 receptor binding analog of claim 12-14 in the method of  
2 claim 25 or 26.

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